REMARKS

The present application is directed to devices and compositions for detecting and diagnosing infectious diseases. In particular, the application relates to the use of a transdermal delivery device to diagnose infectious diseases such as mycobacterial infections. Prior to the issuance of the January 10, 2003 office action, Claims 21-29 were pending. In an effort to facilitate prosecution Claims 21, 23 and 28 have been amended, and Claim 30 has been added. Support for the new claims and amendments can be found generally within the specification. No new matter has been added. Accordingly, following entry of the present amendment Claims 21-30 will be pending.

Drawings

Applicant acknowledges that the informal drawings filed with the application are acceptable for examination purposes only and also notes that the drawings are objected to by the Draftsperson. Applicant will defer formal correction of the noted defects until the application is allowed by the Examiner.

Specification

In the Office Action dated January 10, 2003, the Examiner requested amendment of the specification so that the necessary complete reference to the prior application is provided. Applicant's specification has been amended herein in accordance with the Examiner's recommendation and suggested language. Withdrawal of this rejection is therefore respectfully requested.

Trademark Usage

In the Office Action dated January 10, 2003, the Examiner noted the use of the trademarks "Torriban", "Finn-Chamber", "Perme-aide S" and stated that they should be capitalized wherever they appear and be accompanied by the generic terminology. In accordance with the Examiner's request, the appropriate amendments to the specification have been entered herein. Withdrawal of this rejection is therefore respectfully requested.

Claim Rejections 35 USC §112, second paragraph

In the Office Action dated January 10, 2003, Claims 21-29 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that Claim 21 is vague and indefinite in reciting "the antigen composition is contained in the holding portion for transdermal delivery of the antigen" because it is unclear how the antigen composition is contained or positioned in the holding portion so as to allow for transdermal delivery upon contact with the skin. In an effort to facilitate prosecution, applicant has amended Claim 21 by removing the objectionable language and replacing it with the term "applied". Support for this amendment is found throughout the specification for example on page 22, lines 11-20.

The Examiner stated that Claim 21 lacks antecedent support in reciting "the skin". In an effort to facilitate prosecution, applicant has amended Claim 21 by removing the word "the".

The Examiner stated that Claim 23 is vague and indefinite in reciting "physiologically effective solution" because it is unclear how the solution is rendered "effective (physiologically)". The Examiner further stated that the term "effective" is a subjective term that lacks a comparative basis for defining its metes and bounds. In addition, the Examiner stated that it is further unclear how the physiologically effective solution promotes delivery of the antigen, i.e. transdermal or displacement. In an effort to facilitate prosecution applicant has amended Claim 23 to indicate that a physiologically effective solution is one that allows for transdermal delivery of an antigen in an amount sufficient to generate an immune response.

The Examiner stated that in Claim 28, "polyoxyethyene" should be "polyoxyethylene". Applicant has herein entered the appropriate amendment.

In light of the amendments to claims entered herein, reconsideration and withdrawal of the rejections under 35 U.S.C. 112, second paragraph are respectfully requested.

Claim Rejections 35 USC §103

In the January 10, 2003 Office Action the Examiner stated that Claim 24 is rejected under 35 U.S.C. §103(a) as being unpatentable over Katsuhide *et al.* (JP 09206092, electronic translation version) in view of (1) Haga *et al.* (Tubercle and Lung Disease, June 1994, Supp. No. 1 (196), hereinafter "Haga-I" or (2) Haga *et al.* (Jpn. J. Med. Sci., Biol, 1996), hereinafter "Haga-II" .

According to the Office Action Katsuhide *et al.* disclose a transdermal delivery device comprising an antigen composition including a phosphate buffered solution for promoting transdermal delivery of the antigen, and a holding portion, i.e. plaster, which contains the antigen composition for use in delayed-hypersensitivity reaction measurement and wherein infectious disease such as tuberculosis can be diagnosed therewith. The Office Action stated that the mycobacterial antigens disclosed in Katsuhide *et al.* include MPB64, MPB59, MPB70 and MPB80. In addition, the Office Action stated that Katsuhide *et al.* teach incorporating the composition with hydrophilic ointments such as glycerol or polyethylene glycol, infiltrated into a strap or plaster for contact and application onto skin of human or animal, a patch test, *i.e.*, to effect transdermal delivery of the antigen. After topical application of the ointment into the skin by a patch, an allergic reaction in the form of a hardening phenomenon on the skin is caused by the existence of the antibody to the said mycobacterial antigens.

Also, according to the Office Action, whereas Katsuhide *et al.* fail to disclose that the antigen is derived from mycobacteria such as *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellular*, *Mycobacterium kansaii*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium leprae*, *Mycobacterium africanum*, and *Mycobacterium microti*, Haga-I teach a mycobacterial protein, MPB64, which is isolated from *Mycobacterium bovis*. In addition Haga-1 further teach that MPB64 is also detected in other mycobacterial species such as *Mycobacterium tuberculosis*, *Mycobacterium africanum*, and *Mycobacterium microti*. Furthermore, the Examiner stated that Haga-II showed that detection of MPB64 by delayed skin reaction correlated well with development of tuberculosis in guinea pigs.

Based on the foregoing, the Examiner stated that it would have been obvious to one skilled in the art to isolate, derive and identify MPB64 from mycobacterial species such as taught by Haga-I for incorporation into the transdermal device taught by Katsuhide *et al.* and furthermore to incorporate the teachings of Haga-II therein. Applicant respectfully traverses.

The novel feature of applicant's invention is the ability of the transdermal diagnostic patch to detect active disease. Unlike applicant's invention, the cited references neither individually nor collectively teach the ability to distinguish between an active mycobacterial infection versus a prior immunologic exposure. Accordingly, because the cited references fail to disclose the novel aspect of applicant's invention, they fail to render the invention obvious.

Applicant would like to respectfully point out that "tuberculosis development" is different from 'tuberculosis infection." Applicant believes that the Office Action has confused these two issues. Approximately only 10% of tuberculosis-infected persons develop the disease "active tuberculosis." However, over 90% will become immune and will not develop tuberculosis. The present invention is able to distinguish active tuberculosis patients from immune or vaccinated patients. The classic tuberculin reaction is positive in both tuberculosis patients and those who are immune or vaccinated. The device and composition claimed in the present application are able to distinguish these two groups. In contrast, Haga-II tested the specificity of MPB64 to tuberculosis in guinea pigs by "intradermal injection" which was an invasive method. The Applicant has shown that guinea pigs respond well to intradermal injections of MPB64, but humans do not. Furthermore, Applicant has demonstrated that tuberculosis patients do not respond to intradermal injections of MPB64. In contrast, these tuberculosis patents do respond to MPB64 by transdermal application (the patch test of the present invention). Applicant asserts that one skilled in the art would not have recognized this important aspect of the present invention by examining Katsuhide *et al.*, in view of Haga-II. Applicant asserts that these references, alone or in combination, do not teach the critical aspects of the present invention *i.e.* the ability to distinguish active tuberculosis from immune or vaccinated patients, nor that the transdermal method is critical to the diagnosis and

differentiation of these two patent population groups. Applicant therefore respectfully requests reconsideration and withdrawal of these rejections under 35 U.S.C.§103(a).

Claim 28 was rejected under 35 U.S.C. §103(a) as being unpatentable under Katsuhide *et al.* in view of Barchfield *et al.* (U.S. 5,709,879). The Examiner stated that Katsuhide *et al.* fail to teach polyoxyethylene sorbitan derivative as surfactant for use in the instant invention. Barchfieild *et al.* however disclose a combination of adjuvant components, *i.e.*, liposome/antigen components and emulsion components which act together to produce elevated immune responses. The Examiner stated that one of ordinary skill in the art at the time of the invention would have a reasonable expectation of success in incorporating the teaching of Barchfield *et al.* in combining specific surfactants into the transdermal device of Katsuhide *et al.* because Barchfield *et al.* specifically teach that TWEEN® surfactants are commercially known agents for use in adjuvant combinations. Applicant respectfully traverses for the following reasons.

Applicant maintains that Barchfield *et al.* specifically teach adjuvant formulations comprising two components: an antigen/liposome component and an oil-in-water emulsion. The liposomes are used in embodiments known as fusogenic liposomes wherein they fuse to a biological membrane. Furthermore, Barchfield *et al.* specifically teach a liposome or emulsion composition which is administered systemically and not administered transdermally (see for example column 27, lines 35-54). Applicant maintains that one skilled in the art would not have combined Barchfield *et al.* with the composition and methodology of Katsuhide *et al.* Applicant asserts that the combination of these references does not teach or suggest the transdermal diagnostic device of the present invention. Applicant therefore respectfully requests withdrawal of this rejection.

Conclusion

In conclusion, Applicant believes that the claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited. If the Examiner believes any informalities remain in the application, which may be corrected by Examiner's Amendment, whether any other issues can be resolved by telephone

interview, telephone call with the undersigned attorney at (404) 745-2463 is courteously solicited.

Respectfully submitted,

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